Claims Pending	Allowed Claims of the '983 Patent
1. A method of treating a disease condition in a subject comprising: administering a mixture of L-arginine and an inhibitor of Hmg-CoA reductase to said subject.	1. A method of treating a disease condition in a subject by vasodilation or vasorelaxation comprising: selecting a subject; administering a mixture of L-arginine and an inhibitor of Hmg-CoA reductase wherein said inhibitor of Hmg-CoA reductase is selected from the "Markush Group"; obtaining periodic indicators of vasorelaxation for the subject; and continuing administration of the mixture until a desirable state of vasorelaxation is obtained.
2. Identical to claim 2.	2. Identical to claim 2.
3. Identical to claim 3.	3. Identical to claim 3.
4. Identical to claim 4.	4. Identical to claim 4.
5. Identical to claim 5.	5. Identical to claim 5.
6. The method of claim 5, wherein L-arginine and said inhibitor of Hmg-CoA reductase are administered at a therapeutic concentration.	6. The method of claim 5, wherein L-arginine and said inhibitor of Hmg-CoA reductase are administered at a therapeutic concentration.
12. A therapeutic mixture of a substrate of NOS and an inhibitor of Hmg-CoA reductase.	13. A therapeutic mixture comprised of an inhibitor of Hmg-CoA reductase and a substrate of NOS, said substrate of NOS being a biological equivalent of arginine, said inhibitor being selected from the "Markush Group."
13. The therapeutic mixture of claim 12, which said substrate of NOS is a biological equivalent of L-arginine.	13. See claim 13 above for "biological equivalent of arginine language."

16. A method of stimulating Nitric Oxide Synthase, said method comprising: administering L-arginine and an Hmg-CoA reductase inhibitor.	17. A method of stimulating nitric oxide synthase to produce nitric oxide, said method comprising: administering L-arginine and an agonist of nitric oxide sythase to a subject have a nitric oxide sythase receptor site, said agonist being different than L-arginine and being selected from the "Markush Group" stimulating said nitric oxide synthase to a desirable level with said agonist of nitric oxide synthase.
17. The method of claim 16, wherein said L-arginine is in excess to said Hmg-CoA reductase inhibitor.	18. The method of claim 17, wherein said L-arginine in excess to said agonist.
18. The method of claim 16, wherein a therapeutically effective amount of said L-arginine is combined with a therapeutically effective amount of said Hmg-CoA reductase inhibitor prior to said administration.	19. The method of claim 17, wherein therapeutically effective amounts of L-arginine is combined with therapeutically effective amounts of said agonist prior to administering to the patient.
19. The method of claim 1, further including the step of obtaining periodic indicators of vasorelaxations for the subject; and continuing administration of the mixture until a desirable state of vasorelaxation is obtained.	Corresponds to portions of claim 1 above.
20. The method of claim 1 wherein said inhibitor of Hmg-CoA reductase in atorvastatin	See Remarks.
21. The method of claim 1 wherein said inhibitor of Hmg-CoA reductase is cerivastatin.	See Remarks.
22. The therapeutic mixture of claim 12, wherein said inhibitor of Hmg-CoA reductase is an agonist of NOS.	14. The therapeutic mixture of claim 13, wherein said inhibitor of Hmg-CoA reductase is an agonist of NOS.

23. The therapeutic mixture of claim 12, wherein said inhibitor of Hmg-CoA reductase is atorvastatin.	See Remarks.
24. The therapeutic mixture of claim 13, wherein said inhibitor of Hmg-CoA reductase is atorvastatin and said biological equivalent of L-arginine is L-arginine.	See Remarks.
25. The therapeutic mixture of claim 12, wherein said inhibitor of Hmg-CoA reductase is cerivastatin.	See Remarks.
26. The therapeutic mixture of claim 13, wherein said inhibitor of Hmg-CoA reductase is cerivastatin and said biological equivalent of L-arginine is L-arginine.	See Remarks.

Although it is strongly believed that the comparison above provides ample opportunity to ascertain the allowable nature of this RCE, the three primary above issues which Applicant's attorney is attempting to address in this RCE (RCE of U.S. Ser. No. 09/419,517, itself a continuation of the '983 patent) are discussed below.

I. "Unnecessary Language"

The initial issue is the elimination of the language used in the issued method claims of the '983 patent, including "selecting a subject..." and "obtaining periodic indicators of vasorelaxation..." and other related language. This language was excluded from the independent claims, and now appears in dependent claim 19 because it is not necessary for the patentability of the method claims, as is evidenced by the allowed composition claims in the '983 patent. Accordingly, the Applicant is attempting to clarify the metes and bounds of his invention by removal of this language and its introduction into a dependent claim format.

II. "Genus inhibitors of Hmg-CoA reductase"

The second issue focuses on a claim to the genus "inhibitor of Hmg-CoA reductase." During the prosecution of the '983 patent, the Examiner found an isolated reference purportedly

disclosing the combination of L-arginine and Hmg-CoA reductase inhibitor (Morris *et al*). To facilitate allowance, each of the independent claims of the '983 patent used Markush language specifically identifying each Hmg-CoA reductase inhibitor claimed. The claim limitations were proposed with the caveat that broader claims could be pursued in a later filed application. It is respectfully submitted that the Applicant is entitled to the genus of Hmg-CoA reductase inhibitors for both the method claims and composition claims directed to a therapeutic composition as presented in the pending claims. With regard to the method claims, it is clear that no prior art reference exists which would anticipate or make obvious the combination of L-arginine and an inhibitor of Hmg-CoA reductase for treating a disease condition. With regard to the composition claims, it is respectfully submitted that inclusion of the term "therapeutic" breathes meaning and life into the claim; therefore, this limitation should be duly considered. Examiner Jones is well aware of the case law surrounding *In re Duva* and *In re Thuau*, as well as *In re Craig*; therefore, the case law will not be reasserted. The list provided in the application was not restrictive but rather inclusive and illustrate the Hmg-CoA reductases that could be employed in combination with L-arginine to satisfy the present invention.

III. "Two Additional Species"

The third issue is the inclusion of two additional species. Applicant's attorney has included two additional Hmg-CoA reductase inhibitors (i.e., cerivastatin and atorvastatin) in dependent claim format (see claims 20, 21, and 23 – 26) in the present application. These Hmg-CoA reductase inhibitors were known in the art at the time the application was filed. The present application was filed as a continuation rather than a continuation-in-part because no new matter has been added by including these two additional Hmg-CoA reductase inhibitors. As the Examiner knows, Applicant is not required to teach that which is known in the art, but rather is encouraged to limit the disclosure to that which is necessary to practice and understand the invention. Furthermore, it is respectfully submitted that the inclusion of these additional statins is not violative of the written description requirement. Applicant states in the specification that "L-arginine may be used in conjunction with virtually any of the family of those substances known as HmG-CoA reductase inhibitors" (page 9, lines 13-14), and that the specific listing of inhibitors of HmG-CoA is "by way of example only". Species falling within the genus were disclosed, as was the genus. Accordingly, it is respectfully submitted that no new matter is

introduced by these claims, and that the present application is properly deemed a continuation of the '983 patent.

In an attempt to be fully responsive, each of the issues raised in the previous office action are addressed herein. It is respectfully submitted that all of the pending claims (claims 1-6, 12, 13 and 16-26) are in condition for final allowance.

In the Final Office Action, Examiner Kim rejected claims 1-6, 12, 13, 19 and 22 under 35 U.S.C. §103(a) for being obvious over U.S. Patent No. 5,140,012 to McGovern *et al* ("McGovern ") in view of U.S. Patent No. 5,634,895 to Igo *et al* ("Igo"). The stated basis for the obviousness rejection of claims provided in the Office Action is that McGovern purportedly teaches a method for preventing onset of restenosis after angioplasty employing a Hmg-CoA reductase inhibitor, pravastatin, and that lovastatin reduces restenosis following angioplasty. In addition, Igo purportedly teaches a method of treating restenosis by administering a nitric oxide donor agent including L-arginine. In the opinion of the Examiner, to employ the combination of L-arginine and Hmg-CoA reductase inhibitor to treat restenosis "would have been obvious because all of the components are well known individually for treating restenosis following angioplasty." Applicant respectfully disagrees, believing that the Examiner has not established a prima facie case of obviousness.

It is respectfully submitted that neither McGovern nor Igo suggests Applicant's claimed invention. Restenosis is a broad medical term that involves the reparative response to injury after angioplasty. It is respectfully asserted that the purpose provided in the art of administering a Hmg-CoA reductase inhibitor (i.e., pravastatin) is to reduce serum cholesterol to thereby reduce platelet aggregation (see e.g., column 2, line 41-43 of McGovern), and the purpose of administering L-arginine is to form NO thereby reducing vasoconstriction (see e.g., column 7, lines 6-18 of Igo). Thus, it can hardly be said that pravastatin and L-arginine were known for the same purpose. Accordingly, even assuming arguendo that pravastatin and L-arginine are described in the art as set forth by the Examiner, these teachings do not satisfy a prima facie case of obviousness. The two claimed elements (e.g., L-arginine and pravastatin) are not used for the same purpose. Thus, the idea of combining them would not flow logically from the individual teachings.

Applicant suggests administering these agents to enhance nitric oxide availability. Neither McGovern nor Igo provides any motivation to actually deliver L-arginine and an agent

that enhances nitric oxide production. Absent such motivation or suggestion, it is improper to combine the references in support of an obviousness rejection under 35 U.S.C. § 103. Only through Applicant's teaching is one motivated to administer both L-arginine and an agent that enhances NO production (e.g., via enhanced conversion of L-arginine into NO). The Federal Circuit has consistently held that in order to establish a proper prima facie case of obviousness, the PTO must show a motivation apart from the teaching of the invention to combine the references. Since neither reference suggests or teaches a reason for the combination of either agent with the other, it is respectfully submitted that a prima facie case of obviousness has not been established. The Federal Circuit, in a recent case, *In re Rouffet*, reversed an obviousness rejection where, as in this case, the Examiner improperly pieced together elements in the prior art when there was no motivation to do so. 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998). There is no suggestion in McGovern that there would be any benefit or advantage gained by combining a Hmg-CoA reductase inhibitor and L-arginine. Nor is there any suggestion or teaching in Igo that L-arginine would provide any added benefit to a Hmg-CoA reductase inhibitor formulation. Accordingly, the rejection should be withdrawn.

The Examiner also rejected claims 2, 5, 6, 19 under 35 U.S.C. § 103(a) as being obvious since they are within the knowledge of the skilled pharmacologist and conventional routes of administration. These dependent claims should be allowed based upon their dependency on the claims presented above that are in condition for allowance.

Additionally, the Examiner has rejected claims 1, 2, 5, 12, 13, 20, 21 and 24-26 under 35 U.S.C. §103(a) for being obvious over Wang *et al* (1994) ("Wang"), Pharmacol. Res. (1996) ("the U reference") and U.S. Patent No. 6,093,719 to Bocan ("Bocan"). The stated basis for the obviousness rejection of claims provided in the Office Action is that Wang purportedly teaches dietary L-arginine prevents atherogenesis in the coronary artery of the hypercholesterolemic rabbits. The Examiner states that the U reference teaches that cerivistatin interferes with a major process involved in atherogenesis and Bocan teaches that atorvastatin alone results in a less atherogenic lipoprotein profile. In the opinion of the Examiner, "combinations of L-arginine and cerivistatin or atorvastatin to treat a condition such as atherogenesis would have been obvious because all of the components are well known individually for treating atherogenesis." Applicant respectfully disagrees.

As presented in the arguments above, it is respectfully asserted that the purpose provided in the art of administering a Hmg-CoA reductase inhibitor (i.e., atorvastatin) is to reduce serum cholesterol to thereby reduce platelet aggregation (see e.g., column 2, lines 46-51 of Bocan), and the purpose of administering L-arginine is to form NO thereby reducing vasoconstriction (see e.g., abstract of Wang). Accordingly, even assuming arguendo that cerivistatin, atorvastatin, and L-arginine are described in the art as set forth by the Examiner, these teachings do not satisfy a prima facie case of obviousness. The two claimed elements (e.g., L-arginine and cerivistatin / atorvastatin) are not used for the same purpose, and the idea of combining them would not flow logically from the individual teachings.

Furthermore, neither Wang nor Bocan provides any motivation to combine L-arginine and a Hmg-CoA reductase inhibitor. Absent such motivation or suggestion, it is improper to combine the references in support of an obviousness rejection under 35 U.S.C. §103. See the discussion above. Bocan is directed towards a method of treatment of atherosclerosis, which will restore endogenous vascular endothelium-dependent activities. However, this is due to ACAT and an Hmg-CoA reductase inhibitor working to decrease the adherent properties of the vessel walls. Again, Bocan fails to recognize any role that an Hmg-CoA reductase inhibitor plays in activation of NOS to result in vasodilation.

The Examiner has rejected claims 3 and 4 under 35 U.S.C § 103(a) for being obvious in light of MacAllister *et al* (1996) ("MacAllister"). The stated basis for the obviousness rejection of claims provided in the Office Action is that MacAllister teaches that cardiovascular diseases, such as hypertension, result from abnormalities of the L-arginine:NO pathway and accelerates atherogenesis. In the opinion of the Examiner, one of ordinary skill in the art would have been motivated to combine both agents to treat the disease conditions claimed since each of the agents are useful in treating diseases related to cardiovascular and coronary blood vessels caused by atherogenesis. Again, Applicant respectfully disagrees.

MacAllister does not teach or contain any reference to Hmg-CoA reductase inhibitors, nor is there any suggestion that Hmg-CoA reductase inhibitors are agonists of NOS. MacAllister does not provide any motivation to combine L-arginine and Hmg-CoA reductase inhibitors and does not discuss the role that L-arginine plays in combination with Hmg-CoA reductase inhibitors, which is the fundamental discovery of the Applicant. This rejection is improper and should be withdrawn.

The Examiner has rejected claim 19 under 35 U.S.C § 103(a) for being obvious in light of for Lefer *et al* (1993) ("Lefer"). The stated basis for the rejection of claims provided in the Office Action is that Lefer teaches that Hmg-CoA reductase inhibitor and L-arginine attenuated both the reduced basal NO production and increased adhesiveness of endothelium resulting from the administration of L-NAME, a blocker of NOS. The stated basis of the rejection is that the use of the combination of agents to stimulate NOS would be inherent because each are individually known to attenuate the effects of L-NAME.

The arguments presented above apply equally well to this rejection. Lefer purportedly suggests that individually, L-arginine or an Hmg-CoA reductase inhibitor reduce the effects of L-NAME on NO production. There is no suggestion that L-arginine conversion to NO is enhanced by Hmg-CoA reductase inhibitors.

CONCLUSION

In conclusion, it is respectfully requested that the Examiner specifically address the issues presented in this application and pass this case to issue. In view of the remarks presented above, it is believed that pending claims 1-6, 12, 13, and 16-22 are in condition for allowance and notice to such effect is respectfully requested. Should the Examiner have any questions regarding the above, the Examiner is invited to contact the undersigned at his convenience.

Respectfully submitted,

Dated: By: _____

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